For Health Professionals.

Prescribing and Adverse Event reporting information

Dovato
dolutegravir/lamivudine

POWER REIMAGINED

AN INNOVATIVE, GUIDELINE-RECOMMENDED REGIMEN FOR YOUR PATIENTS LIVING WITH HIV

- **POWERFUL, DURABLE EFFICACY**[1,2]
- **HIGH BARRIER TO RESISTANCE**[1,2]
- **TDF, TAF AND ABC FREE**

DOVATO is indicated for the treatment of HIV-1 in adults and adolescents above 12 years weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

GOING BEYOND SUPPRESSION

gemini 1 gemini 2

METABOLIC PARAMETERS AND BIOMARKER CHANGES AT 144 WEEKS

DOVATO vs DTG + TDF/FTC in treatment-naïve patients[1]

	Changes in bone turnover biomarkers significantly favour DOVATO vs DTG + TDF/FTC[1] The GEMINI studies did not determine whether these changes translate to clinical differences.
	Changes in renal function biomarkers significantly favour DOVATO vs DTG + TDF/FTC[1] The GEMINI studies did not determine whether these changes translate to clinical differences. Renal-related AEs leading to withdrawal were comparable across both arms.[1]
	Improvements in TC/HDL ratio occurred in both arms, with a statistically greater reduction in the DTG + TDF/FTC arm[1]
	Overall mean weight change from baseline was +3.7 kg in the DOVATO arm and +2.4 kg in the DTG + TDF/FTC arm[1]

TANGO

CHANGES IN METABOLIC PARAMETERS AT 48 WEEKS AFTER SWITCHING FROM TAF-CONTAINING REGIMENS

DOVATO vs TAF-containing regimens in virologically suppressed patients[2-4]

	INSULIN RESISTANCE SIGNIFICANTLY FEWER patients with insulin resistance* after switching to DOVATO from a TAF-containing regimen[2]
	LIPIDS SIGNIFICANT IMPROVEMENTS in most lipid parameters in the DOVATO arm vs the TAF-containing regimens arm, including TC/HDL ratio[2]
	BONE AND RENAL BIOMARKERS MINIMAL CHANGES in bone turnover and renal function biomarkers across both arms[2,3†]
	WEIGHT GAIN AND METABOLIC SYNDROME OBSERVED SIMILAR[4‡]: • Small increases in mean weight (≈0.8 kg) in both arms • Increases in metabolic syndrome‡ • Median changes in fasting glucose and HbA_{1c}

DTG 50 mg + 3TC 300 mg used in the GEMINI studies.
*Defined as homeostatic model assessment of insulin resistance (HOMA-IR) ≥2.[2]
†Longer-term data required to determine clinical impact of switching to DOVATO from TAF-containing regimens.
‡Defined by the International Diabetes Federation as a combination of risk factors for cardiovascular disease.[5]

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Date of preparation: April 2021 PM-GBL-DLL-WCNT-200014 v2

Received: 1 July 2021 | Accepted: 8 July 2021

DOI: 10.1111/hiv.13152

ORIGINAL RESEARCH

Decrease of condom use in heterosexual couples and its impact on pregnancy rates: the Swiss HIV Cohort Study (SHCS)

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Funding information
This study has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant no. 177499), by SHCS project no. 824 and by the SHCS research foundation. The data are gathered by the five Swiss university hospitals, two cantonal hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

Abstract

Introduction: Following the 'Swiss statement' in 2008 it became an option to omit the use of condoms in serodiscordant couples and to conceive naturally. We analysed its impact on condom use and pregnancy events.

Methods: In all, 3023 women (aged 18–49 years) participating in the Swiss HIV Cohort Study were included. Observation time was divided into pre- and post-Swiss statement phases (July 2005–December 2008 and January 2009–December 2019). We used descriptive statistics, Poisson interrupted time series analysis for pregnancy incidence, and logistic regression to identify predictors of live births, spontaneous and induced abortions.

Results: Condomless sex in sexually active women increased from 25% in 2005 to 75% in 2019, while pregnancy incidence did not. Women after 2008 experienced higher spontaneous abortion rates (12.1% vs. 17.2%, $p = 0.02$) while induced abortion and live birth rates did not change significantly. Spontaneous abortions were more common in older women [adjusted odds ratio (aOR) = 1.4, 95% CI:

*These authors contributed equally to this work.

†The members of the Swiss HIV Cohort Study are given in Appendix 1.

1.2–1.7, $p < 0.001$], in women consuming alcohol (aOR = 2.8, 95% CI: 1.9–4.1, $p < 0.001$) and in those with non-suppressed viral load (aOR = 0.2, 95% CI: 0.1–0.4, $p \leq 0.001$). Induced abortions were more likely in women with depression (aOR = 3.4, 95% CI: 1.8–6.3, $p < 0.001$) and non-suppressed viral load (aOR = 0.3, 95% CI: 0.2–0.7, $p = 0.003$).

Conclusions: The publication of the Swiss statement resulted in more condomless sex in heterosexual women, but this did not result in a higher incidence of pregnancy. Maternal age and spontaneous abortion rates increased over time, while induced abortion rates were not significantly affected. Women living with HIV in Switzerland have an unmet need regarding family planning counselling.

KEYWORDS

abortion, condom, family planning, HIV, pregnancy

INTRODUCTION

The 2008 'Swiss statement' was an important milestone proclaiming the safety of condomless sex in HIV serodiscordant couples, if the HIV-infected partner was virally suppressed while taking combined antiretroviral therapy (cART) [1,2]. The safety of this approach has been confirmed within the Swiss HIV Cohort Study (SHCS) [3], and additionally in large, fully powered randomized clinical trials and international prospective studies [4,5]. Given this recommendation, couples planning to conceive no longer need to be treated by fertility services. With a suppressed HIV viral load, in the absence of other sexually transmitted infections (STI) and with mutual agreement, unprotected vaginal intercourse was no longer discouraged by treating physicians.

Hasse et al. [3] and Kouyos et al. [6] described increasing rates of condomless sexual intercourse in stable heterosexual relationships in the SHCS following the release of the Swiss statement.

The new era in which condoms are not necessarily needed to avoid HIV transmission has major consequences not only for women who are planning to have children, but also for those who need effective contraception. A recent analysis of Swiss data has shown low contraceptive use and high rates of unplanned pregnancies in women living with HIV (WLWH) [7].

Hence, birth control has become an important topic in providing care for WLWH. It is of great importance to avoid unplanned pregnancies in WLWH, as they are often associated with adverse outcomes such as unsafe abortions, pregnancy complications (e.g. pregnancy-related sepsis), mother-to-child transmission of HIV and mortality due to non-pregnancy-related infections [8,9].

Currently it is unclear if the high rate of unintended pregnancies in the SHCS has changed over time, and whether it was influenced by the reduced condom use following the publication of the Swiss statement in 2008.

We therefore aimed to provide a detailed analysis of obstetric events in the SHCS. In the first instance, we analysed pregnancy incidence between July 2005 and December 2019, its correlation with condom use and characteristics of women of childbearing age. Second, we assessed the impact of the Swiss statement on condom use and obstetric events, and finally we examined the risk factors for live births as well as for spontaneous and induced abortions.

METHODS

Swiss HIV Cohort Study (SHCS)

The SHCS (www.shcs.ch) is a prospective cohort study with ongoing enrolment of HIV-positive adults in Switzerland. It has remained representative of the HIV patient population since its inception in 1988, and currently covers at least 75% of all patients receiving cART and 69% of patients living with AIDS in Switzerland [10]. Around 25% of all SHCS participants are female. Detailed information on demographics, mode of HIV acquisition, risk behaviour, clinical events, coinfections and treatment is collected at registration and then at 6-monthly intervals. Local ethical committees of all participating study sites have approved the study, and written informed consent is obtained from all participants. Information on obstetric events and on oral hormonal contraception has been routinely collected since July 2005 and June 2007, respectively.

Study population, observation time and definitions

In the first part of the analyses, dedicated to examining the occurrence of obstetric events, we included all heterosexual women of childbearing age (18–49 years) participating in the SHCS cohort with at least one study visit between July 2005 (start of obstetric event information collection) and December 2019. In the second part, we assessed the impact of the Swiss Statement on condomless sex and obstetric events. For this purpose, we divided the observation time in a pre-Swiss statement period (phase 1), from July 2005 to December 2008, and a post-Swiss statement period (phase 2) from January 2009 to December 2019. The third part focused on identifying contemporary predictors of pregnancy outcomes and included only women with at least one obstetric event between January 2009 and December 2019.

Exclusion criteria were menopause (before the age of 49), hysterectomy and tubal ligation.

The term obstetric event was used to describe pregnancy outcomes defined as pregnancies ending in (i) live birth, (ii) spontaneous or (iii) induced abortion. Education was defined as 'low' if no or only mandatory school was completed, 'medium' if an apprenticeship or bachelor degree was completed, or 'high' if a higher professional qualification or university qualification was completed. Alcohol consumption was defined as any level of consumption during pregnancy. Hormonal contraception was counted if reported at any time during the observation period, irrespective of the duration. Having an HIV viral load ≤ 400 copies/mL was considered as viral suppression (the threshold of 400 copies/mL was set because of the different levels of detection available over time). The ART regimens were defined as integrase inhibitor-based (INSTI), protease inhibitor-based (PI), and nonnucleoside-reverse transcriptase inhibitor-based (NNRTI), each combined with one or two nucleoside reverse transcriptase inhibitors (NRTIs) and as second-line treatment (if they contained more than one INSTI, PI or NNRTI other than ritonavir).

Clinical and behavioural characteristics were recorded at the first study visit after an obstetric event, therefore reflecting the last 6 months before the study visit.

Statistical analyses

We first described the total number and rates of obstetric events among women of childbearing age over time, and correlated them with both age and condom use in women in stable partnerships. We then compared the socio-epidemic characteristics of women of childbearing age between phase 1 and phase 2. Group comparisons of categorical variables were investigated using the χ^2 test, with continuous variables assessed using the Wilcoxon rank-sum test. Mixed-effect Poisson interrupted time series (ITS) models were fitted to determine the trends in pregnancy incidence (per 100 women-years), with random intercept effect per woman to adjust for women having multiple events, and 1 January 2009 as the date intervention (i.e. approximately a 1-year lag from the date of the Swiss statement). In the third part of the analysis, we compared demographic and clinical characteristics of women with an obstetric event according to the pregnancy outcome, using the χ^2 test and the Kruskal–Wallis test to determine group differences. To identify predictors of live birth and risk factors for spontaneous and induced abortions, we additionally performed uni- and multivariate logistic regression analyses. We fitted models comparing live births with spontaneous abortions and then live births with induced abortions, with independent variables for age at obstetric event, ethnicity, risk group [heterosexual (reference), IVDU, blood transfusion, perinatal transmission, other] and stable partnership (yes/no), sexual intercourse with a stable partner (yes/no), use of condoms with stable partner, educational level [low (reference), medium, high), suppressed viral load, CD4 count, ART type (NNRTI, PI, INSTI, second-line treatment), time on ART, being in psychiatric care, depression diagnosis and alcohol consumption. Those predictors significant at the 5% level in the univariate analyse were carried over to the multivariate analysis, with forward then backward selection based on the Bayesian information criteria to identify the most parsimonious adjusted model. Results were presented with odds ratios (ORs) and 95% confidence intervals (95% CIs). We did not correct for multiple testing following the analyses. All statistical analyses were performed with R. Version 3.6.1. [11].

RESULTS

Obstetric events in correlation to age and condom use over time

During the study period (July 2005–December 2019) 3023 women of childbearing age were followed in the SHCS. After an initial increase until 2008 we observed a decline in the total number of women of childbearing age from 1831 in 2008 to 994 in 2019, as well as declining total numbers of obstetric events from 111 in 2005 to 40 in 2019 (Figure 1). For those self-declaring that they were sexually active, condomless sex increased from 25% in 2005 to 75% in 2019 ($p < 0.001$). This trend was mainly driven by women having sex with a stable partner. Although the percentage of women having condomless sex with an occasional partner increased from 2% in 2005 to 5% in 2019 ($p = 0.004$) the absolute number was small (Figure 2). Pregnancy incidence decreased slightly from 6.5 (95% CI:

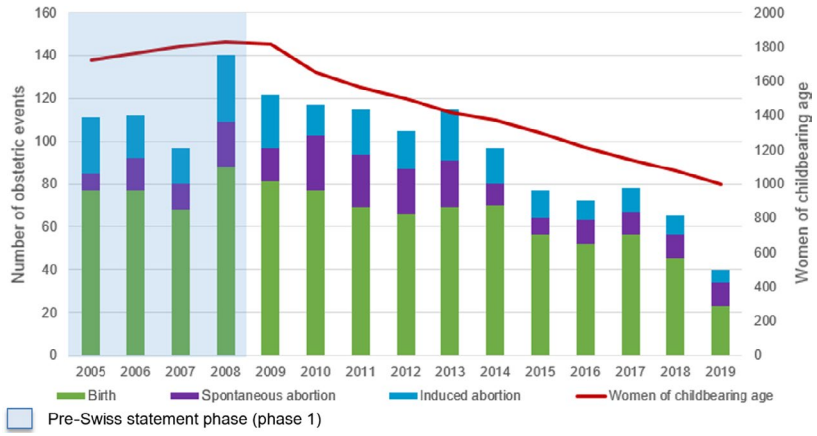

FIGURE 1 Absolute numbers of women of childbearing age and occurrence of obstetric events in the Swiss HIV Cohort Study over time (2005–2019)

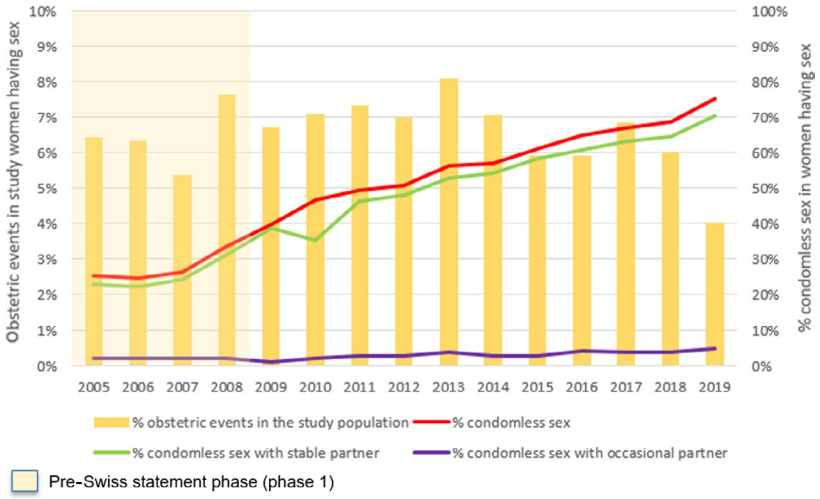

FIGURE 2 Sexually active women of childbearing age having condomless sex and obstetric event rates over time in the Swiss HIV Cohort Study (2005–2019)

5.4–7.9) to 5.4 (4.0–7.0) per 100 women-years ($p = 0.2$) (Figure S1(A)). We found that although the proportion of women over 35 years increased over time, their pregnancy incidence remained stable (Figure S1(B), top panel). By contrast, in the decreasing group of women younger than 35 years, unadjusted pregnancy incidence has been steadily declining over time from 18.4 (95% CI: 14.4–23.3) per 100 women-years in 2010 to 11.2 (6.7–17.4) per 100 women-years in 2019 ($p = 0.03$).

Comparison of demographic characteristics and obstetric events in the pre-Swiss statement and post-Swiss statement periods

We evaluated data from 2125 women in phase 1 (July 2005–December 2008) and 2593 women in phase 2 (January 2009–December 2019). Women in phase 1 were younger [median age 40 years, interquartile range (IQR): 35–44 vs. 42 years, IQR: 37–45, $p < 0.001$], and they were less likely to be black (29.1% vs. 38.3%, $p < 0.001$). In both phases the majority of women acquired HIV by heterosexual intercourse (69.4% and 75.8%%, $p < 0.001$), but in phase 1 women were more often infected with HIV through intravenous drug use (26.0 vs. 16.7%; $p < 0.001$) than those observed in phase 2 (Table 1). Information on the use of oral hormonal contraception was only available in phase 2 and was 35.7% (Table 1). We found 463 obstetric events in phase 1 and 1016 in phase 2, corresponding to the incidence of an obstetric event of 6.5 (6.0–7.1) and 6.9 (6.4–7.3) per 100 women-years respectively ($p = 0.4$). When comparing time periods before and after the Swiss statement, the live birth rate remained stable (67.4% vs. 66.3%, $p = 0.7$), induced abortions slightly decreased (20.5% vs.

TABLE 1 Comparison of demographic characteristics and obstetric events in women of childbearing age between July 2005–December 2008 (phase 1) and January 2009–December 2019 (phase 2)

	Phase 1[a] [*n* (%) unless noted otherwise]	Phase 2[a] [*n* (%) unless noted otherwise]	*p*-value
Women of childbearing age	2125 (100)	2593 (100)	
Age (years) [median (IQR)]	40 (35–44)	42 (37–45)	< 0.001
Ethnicity			< 0.001
White	1288 (61)	1295 (50)	
Black	619 (29)	992 (38)	
Other	215 (10)	301 (12)	
Missing	3 (0)	5 (0)	
HIV-transmission mode			< 0.001
Sexual intercourse	1474 (69)	1965 (76)	
Intravenous drug use	552 (26)	434 (17)	
Perinatal infection	12 (1)	60 (2)	
Other	41 (2)	61 (2)	
Unknown	46 (2)	73 (3)	
Women with a stable partner	1588 (75)	2129 (82)	< 0.001
Women having sex with stable partner	1483 (70)	1990 (77)	< 0.001
Condomless sex with a stable partner	613 (29)	1427 (55)	< 0.001
Women having sex with a casual partner	385 (18)	542 (21)	< 0.001
Condomless sex with a casual partner	79 (4)	213 (8)	< 0.001
Oral hormonal contraception	n.a.	926 (35.7)	NA
Depression	n.a.	907 (35)	NA
Women who became pregnant	460 (100)	1003 (100)	
Pregnancy outcome			
Live birth	312 (67)	664 (66)	0.7
Spontaneous abortion	56 (12)	175 (17)	0.02
Induced abortion	95 (20)	167 (17)	0.07
Age at time of pregnancy [median (IQR)]	31 (27–36)	34 (30–38)	< 0.001

Abbreviations: *n*, number; IQR, interquartile range; na., not assessed.

[a]Phase 1, July 2005–December 2008; phase 2, January 2009–December 2019.

16.4%, $p = 0.07$) and spontaneous abortions increased (12.1% vs. 17.2%) ($p = 0.02$) (Table 1).

Factors associated with pregnancy outcomes

During the study period, 1479 pregnancies were reported: 986 (66.7%) of the pregnancies ended in live births, 231 (15.6%) in spontaneous abortion and 262 (17.7%) in induced abortion (Table 2).

Compared with live births, spontaneous abortions occurred more frequently among older women (aOR = 1.4 per five additional years, 95% CI: 1.2–1.6, $p \leq 0.001$), those with a stable sex partner (aOR = 3.9, 95% CI: 1.5–10.2, $p = 0.007$), those with higher CD4 count (aOR = 1.1 per 100 cells/μL, 95% CI: 1.1–1.2, $p < 0.001$), those on NNRTI treatment (aOR = 1.7, 95% CI: 1.1–2.5, $p < 0.001$) and those who consumed alcohol (aOR = 2.8, 95% CI: 1.9–4,1, $p \leq 0.001$), but were less likely if the HIV viral load was undetectable (aOR = 0.2, 95% CI: 0.1–0.4, $p \leq 0.001$). Analogously, induced abortions were 3.4 times more likely in women with depression (aOR = 3.4, 95% CI 1.8–6.3, $p \leq 0.001$) and when drinking alcohol (aOR = 1.6, 95% CI 1.0–2.4, $p = 0.04$), but less likely among women with suppressed HIV viral load (aOR = 0.3, 95% CI: 0.2–0.7, $p = 0.003$) and those on PI treatment (aOR = 0.3, 95% CI: 0.2–0.5) (Table 3).

Ethnicity, risk group, educational level, condomless sex with a steady partner, certain types of ART (INSTI, second-line treatment), time on ART and psychiatric

TABLE 2 Demographic and clinical factors according to pregnancy outcome

	Live birth [*n* = 986 (66%)]	Spontaneous abortion [*n* = 231 (16%)]	Induced abortion [*n* = 262 (18%)]	*p*-value
Age (years) [median (IQR)]	33 (29–37)	35 (31–39)	32 (27–37)	< 0.001
Risk group [n (%)]				0.2
Sexual intercourse	852 (86)	188 (81)	213 (81)	
Intravenous drug use	50 (5)	14 (6)	15 (6)	
Perinatal infection	24 (2)	6 (3)	13 (5)	
Other	60 (6)	23 (10)	21 (8)	
Ethnicity				0.2
White	306 (31)	84 (36)	70 (27)	
Black	601 (61)	126 (55)	171 (65)	
Other	79 (8)	21 (9)	21 (8)	
Stable partnership	881 (89)	212 (92)	209 (80)	< 0.001
None or lower education	426 (43)	85 (37)	124 (47)	0.1
Suppressed viral load	910 (92)	191 (83)	185 (71)	< 0.001
CD4 count (CD4/μl) [median (IQR)]	517 (378–685)	596 (396–765)	536 (348–739)	0.01
Time on ART (years)	3.9 (0.5–7.8)	5.7 (1.7–9.1)	3.7 (0.7–8.0)	0.01
Alcohol consumption	139 (14)	73 (32)	71 (27)	< 0.001
Depression	33 (3)	17 (7)	24 (9)	< 0.001

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; n, number.

TABLE 3 Univariate and multivariate logistic regression of factors influencing pregnancy continuation

	Live birth versus spontaneous abortion				Live birth versus induced abortion			
	Univariate LR (95% CI)	*p*-value	Multivariate LR (95% CI)	*p*-value	Univariate LR (95% CI)	*p*-value	Multivariate LR (95% CI)	*p*-value
Age at obstetric event (every 5 years)	1.4 (1.2–1.6)	< 0.001	1.4 (1.2–1.7)	< 0.001	ns			
Stable sex partner	4.6 (1.6–12.7)	0.004	3.9 (1.5–10.2)	0.007	3.0 (1.3–6.8)	0.01	ns	
Suppressed HIV load	0.4 (0.3–0.6)	< 0.001	0.2 (0.1–0.4)	< 0.001	0.2 (0.1–0.3)	< 0.001	0.3 (0.2–0.7)	0.003
CD4 count (100 steps)	1.1 (1.0–1.2)	< 0.001	1.1 (1.1–1.2)	< 0.001	ns			
NNRTI-based ART	1.8 (1.3–2.6)	0.002	1.7 (1.1–2.5)	0.01	2.3 (1.6–3.3)	< 0.001	ns	
PI-based ART	0.5 (0.4– 0.7)	< 0.001	ns		0.3 (0.2–0.3)	< 0.001	0.3 (0.2–0.5)	< 0.001
Alcohol consumption	2.8 (2.0–4.0)	< 0.001	2.8 (1.9–4.1)	< 0.001	2.3 (1.6–3.2)	< 0.001	1.6 (1.0–2.4)	0.04
Depression	2.0 (1.2–3.7)	0.02	ns		2.9 (1.7–5.3)	< 0.001	3.4 (1.8–6.3)	< 0.001

Note: Not significant at the 5% level: < all other variable.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; LR, logistic regression; NNRTI, nonnucleoside-reverse transcriptase inhibitor; ns, not significant; PI, protease inhibitor.

care, did not show any associations with pregnancy outcome (Table S1).

DISCUSSION

The proportion of women of childbearing age in the SHCS is steadily decreasing over time, and despite more condomless sex, pregnancy incidence is not increasing over time. Moreover, there is an increase in spontaneous abortions possibly due to the ageing women of our HIV cohort. The rate of induced abortions slightly increased, but remained high and twice the rate reported for HIV-negative women by the Swiss authorities [12]. Women with HIV viral suppression and alcohol abstinence were more likely to have a live birth.

Ageing as a driver of pregnancy rates but not condoms use

The opportunity for serodiscordant couples to conceive through unprotected intercourse, instead of assisted reproduction, and increasing rates of condomless sex in the SHCS did not result in increased incidence of pregnancy over time. However, during the same period, the live birth rates of all women of childbearing age living in Switzerland decreased slightly from 4.5 per 100 person-years in 2009 to 4.8 per 100 person-years in 2019 [13].

With the introduction of cART, WLWH have experienced improved health, longer life expectancy and fewer mother-to-child (vertical) HIV transmissions, with correspondingly increasing live birth rates [14]. Yet, two decades after the introduction of cART, pregnancy rates of WLWH in Switzerland are still low. Our observations are shared by HIV cohorts from low- and middle-income countries [15–17], but data from high-income countries are scarce. Nonetheless, our findings are in line with those of a Canadian study reporting overall lower birth rates in WLWH compared with the HIV-negative general population. Comparable to our data the study authors observed an increasing age of WLWH giving birth. But when observing only women with at least one child, and comparing them with HIV-negative geomatched controls, the differences disappeared [18]. Similarly, a report from the United States showed no differences in pregnancy rates of matched HIV-positive and -negative women in the Women Interagency HIV Study (WIHS) from 2002 onwards [19]. These observations suggest that in a setting of available, effective cART, pregnancy rates might be driven more by sociodemographic than by biological HIV-related factors.

An explanation for the declining numbers of pregnancies in our cohort is the ageing of WLWH in Switzerland, resulting in lower total numbers of women of childbearing age.

The declining pregnancy incidence in our study is instead driven by two different developments: a higher proportion of older women, with lower but constant pregnancy rates, on the one hand, and a steadily declining proportion of younger women with *per se* higher (but in our study over time declining) pregnancy rates on the other. Notably the pregnancy incidence in women under 35 years almost halved between 2010 and 2019.

Besides the fact that pregnancy rates will naturally decrease with increasing maternal age, evidence of lower ovarian reserve, and premature menopause related to HIV is conflicting. Many of the differences seen in earlier reports could not be seen when adjusted for age, body mass index and drug use [20–22]. However, infertility remains an important issue in HIV-positive women. Iyer at al. [15] reported subfertility in two out of three HIV-positive couples in South Africa and elevated risk of infertility compared with HIV-negative women even when on cART. Data on the effects of ART on reproduction have postulated that mitochondrial toxicity of NRTIs directly impacts oocytes, and animal models have demonstrated the embryonal toxicity of zidovudine [23]. Although the positive effect of ART on fertility by treating and preventing symptomatic HIV clearly outweighs the possible adverse effects, it remains unclear if, and the extent to which, the different substances impact fertility.

It also remains unclear how much the steep decline of pregnancy rates among women under 35 is due to an unfulfilled wish to conceive, or to an increasing proportion of young women not wanting to conceive.

Psychological factors and depression might play a role with regard to pregnancy rates. While one in three (35%) women of childbearing age after 2009 in our cohort was diagnosed with a depression, it was only present in 5% of all women who conceived during the study period.

Why do abortions not decrease?

Despite having over 90% of women on cART and virally suppressed, only two in three pregnancies of WLWH in Switzerland ended in a live birth.

EuroSIDA recently reported similar pregnancy outcomes from women across Europe, Argentina and Israel [24]. The proportion of pregnancies ending in a spontaneous abortion in our study increased over time, with unsuppressed HIV load, age and alcohol consumption being associated variables. HI-viral detection as a risk factor for spontaneous abortion has been frequently reported from high- and low-income settings [25–27]. However, studies showing decreasing miscarriage rate with the introduction of cART are lacking. By contrast, Townsend et al. [28] showed unchanged miscarriage rates of 3.9–5.6% in WLWH in the UK and Ireland between 1994 and 2006 despite the introduction of cART. This might be explained by the increasing rate of women diagnosed during pregnancy from 2000 onwards, and the frequent delay of the start of cART until the second trimester. A US study similarly reported no significant trends over the years when age-adjusted, and showed that if on cART and properly matched, HIV-positive and -negative women do not differ in terms of their risk for miscarriages [19]. The rate of women on cART in the SHCS has been steadily increasing and almost 90% of pregnant women between 2009 and 2019 had undetectable viral loads. Thus, although being a recognized risk factor for miscarriage, detectable HIV is unlikely to be the determining factor for the increased rate of spontaneous abortions. In our study, the increasing maternal age seems most likely to be responsible for miscarriages, due to the

higher risk of chromosomal abnormalities with increased age. The median age at time of giving birth in Switzerland is also steadily increasing in HIV-negative women, but to a lesser extent than in HIV-positive women: notably the median age at birth in 2019 was 32 years in HIV-negative versus 37 years in the SHCS [29].

In the years following the introduction of cART, a worldwide decrease of induced abortions was observed. Over the last decade the rates of induced abortions do not seem to have decreased further in contrast to the steadily falling rates among HIV-negative women [19,27,28,30–33]. We found that the rate of induced abortions among WLWH in Switzerland did not decrease from 2005, and is twice the rate of HIV-negative women in Switzerland [12]. This is in accordance with the Women's Interagency Study (WISH) in the US, which reported unchanged abortion rates over time [19]. Stringer et al. [34] notably reported an induced abortion rate from 253 pregnant women from low-income settings in Africa, Asia and America that was inferior to ours in Switzerland (11% vs. 17%). Although we identified viral replication as well as depression as independent risk factors, 71% of the women deciding to terminate their pregnancy in our cohort were virally suppressed and only 9% had a diagnosed depression. Thus, additional factors must be involved. It has been extensively reported that unplanned pregnancies leading to induced abortions in WLWH are very common [35–37]. This, and the fact that 80% of women having an induced abortion were living in a stable partnership, raises the question of availability of effective contraceptives. A recent questionnaire-based SHCS survey of women of childbearing age showed that almost half (43.7%) of sexually active women who were not on contraceptives were not planning to conceive. In the same study, one in six women using contraceptives reported an unplanned pregnancy. Male condoms were still the most frequently used method of contraception (73.4%), whereas we found a very low use of other contraceptives (oral pill, 10.7%; intrauterine device, 9.4%; other long-acting reversible methods, 4.7%) [7]. These data confirm our findings and show that a considerable part of sexually active WLWH in Switzerland do not use contraceptives at all or are using contraceptives that are not able to prevent a pregnancy. The predominance of male condoms and the low rates of hormonal contraceptives in WLWH has also been reported in other studies [38]. One of the reasons might be fear of potential drug–drug interactions (DDIs), which prevents doctors from prescribing hormonal contraceptives. With the available data, we are not able to distinguish between incorrect use of contraceptives and failure due to DDIs, but with the increasing use of INSTIs in the SHCS, which do not interact with hormonal contraceptives [39], DDI as a cause of unintended pregnancies will become less important.

Strengths and limitations

One strength of this study is that it is the first one to explore the occurrence of pregnancies and their outcomes in WLWH in Switzerland. With around 75% of WLWH on cART living in Switzerland included in the cohort and by analysing a period of over 10 years, our data are representative and comprehensive in terms of reflecting the national situation.

Our study has several limitations: due to the late inclusion of data on depression and hormonal contraception in the SHCS, we could not assess its prevalence over time. Data on intrauterine devices to prevent pregnancies are not routinely collected in the SHCS. Moreover, we were not able to distinguish between unfulfilled and nonexistent wish to conceive, as we were not able to differentiate between lack of contraceptives and ineffective contraceptives as reasons for the high rate of induced abortions. Owing to the lack of an HIV-negative control group we could only compare our findings in relation to those of the general population as reported by the Swiss Federal Statistical Office.

CONCLUSIONS

Higher rates of condomless sex following the Swiss statement have not translated into more pregnancies. Instead, increasing age and depression seem to be main factors influencing pregnancy rates, and also the rates of spontaneous and induced abortions in the SHCS. Although almost 90% of women with a pregnancy event have a suppressed viral load, and are in close medical care, the rates of induced abortions have remained twice as high as reported for HIV-negative women in Switzerland. This shows that HIV care services in Switzerland urgently need to improve their family planning counselling and services.

In order to meet the reproductive health needs of WLWH, timely family planning and accessible fertility treatment for those who want to have children, as well as provision of safe and effective contraception for those who do not, need to be integrated into HIV care.

MEETINGS AT WHICH PARTS OF THE DATA WERE PRESENTED

- Decreasing condom use and its impact on obstetric events in the Swiss HIV Cohort Study (SHCS), Oral presentation at EACS 2017 Milan, Italy
- Live births, spontaneous and induced abortions in the Swiss HIV Cohort Study (SHCS): Which factors may predict pregnancy outcomes? Poster presentation at HIV Drug Therapy 2018, Glasgow, UK

ACKNOWLEDGEMENTS

We thank all patients, doctors and nurses associated with the SHCS. We also thank Andri Rauch for his advice regarding additional calculations and structure of the manuscript.

CONFLICTS OF INTEREST

None of the authors has declared a possible conflict of interest related to the study.

AUTHOR CONTRIBUTIONS

AH, KA-P and AA]developed and designed the study. AA planned and performed the statistical analyses. AH wrote the manuscript with supervision and input from KA-P and AA. AC, BMdeT, BH, PP, CRK NB-B and MS contributed with their professional expertise, and reviewed and discussed the analyses and the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Hachfeld A, Atkinson A, Calmy A, et al. Decrease of condom use in heterosexual couples and its impact on pregnancy rates: the Swiss HIV Cohort Study (SHCS). *HIV Med*. 2021;00:1–10. https://doi.org/10.1111/hiv.13152

APPENDIX 1

Members of the Swiss HIV cohort study

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